



Comparison of the efficacy of equivalent doses of dexamethasone, methylprednisolone, and hydrocortisone for treatment of COVID-19-related acute respiratory distress syndrome: a prospective three-arm randomized clinical trial

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Summary

Background This prospective controlled clinical trial aimed to compare the efficacy of methylprednisolone, dexamethasone, and hydrocortisone at equivalent doses in patients with severe COVID-19.

Methods In total, 106 patients with mild to moderate COVID-19-related acute respiratory distress syndrome (ARDS) were randomized to receive either dexamethasone (6 mg once a day), methylprednisolone (16 mg twice a day), or hydrocortisone (50 mg thrice a day) for up to 10 days. All participants received a standard of care for COVID-19. The primary and secondary efficacy outcomes included all-cause 28-

day mortality, clinical status on day 28 assessed using the World Health Organization (WHO) eight-category ordinal clinical scale, number of patients requiring mechanical ventilation and intensive care unit (ICU) care, number of ventilator-free days, length of hospital and ICU stay, change in PaO₂:FiO₂ ratios during the first 5 days after treatment, and incidence of serious adverse events. *P*-values below 0.008 based on Bonferroni's multiple-testing correction method were considered statistically significant.

Results According to the obtained results, there was a trend toward more favorable clinical outcomes in terms of needing mechanical ventilation and ICU care, number of ventilator-free days, change in PaO₂:FiO₂ ratios during the first 5 days after treatment, clinical status score at day 28, length of ICU and hospital stay, and overall 28-day mortality in patients receiving dexamethasone compared to those receiving methylprednisolone or hydrocortisone; however, likely due to the study's small sample size, the difference between groups reached a significant level only in the case of clinical status score on day 28 (*p*-

Trial registration The trial was registered at Clinicaltrials.gov (registration number: IRCT20120215009014N354). Registration date: 2020-05-12.

Availability of data and material The corresponding author had full access to all datasets used and analyzed in this study. The datasets are available from the corresponding author upon reasonable request up to 2 years after publication.

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value=0.003). There was no significant difference in the incidence of serious adverse events between the study groups.

Conclusion Based on the results, severe cases of COVID-19 treated with dexamethasone might have a better clinical status at 28-day follow-up compared to methylprednisolone and hydrocortisone at an equivalent dose. Larger multicenter trials are required to confirm our findings.

Keywords Severe COVID-19 pneumonia · SARS-CoV-19 infection · Corticosteroids · Cytokine storm · Mechanical ventilation · Mortality

Abbreviations

| | |
|------------------------------------|---|
| ANOVA | One-way analysis of variance |
| ARDS | Acute respiratory distress syndrome |
| COVID-19 | Coronavirus disease 2019 |
| ECMO | Extracorporeal membrane oxygenation |
| ICU | Intensive care unit |
| IL | Interleukin |
| ITT | Intention-to-treat |
| PaO ₂ /FiO ₂ | Arterial oxygen partial pressure to fraction of inspired oxygen ratio |
| RT-PCR | Polymerase chain reaction |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| TNF | Tumor necrosis factor |

Coronavirus disease 2019 (COVID-19), a respiratory syndrome disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected millions of people worldwide. Despite the success of the SARS-CoV-2 vaccine development, the disease remains a major health challenge around the world [1]. The clinical severity of COVID-19 is highly variable, ranging from asymptomatic or mild respiratory illness to severe pneumonia, hypoxemic pulmonary failure, multisystem organ dysfunction, and death [2]. Severe acute lung injury, known as acute respiratory distress syndrome (ARDS), is the most serious complication of COVID-19, which is associated with a high mortality rate. It is characterized by respiratory distress associated with hypoxemia and bilateral infiltrates on chest imaging [3]. Although the pathophysiology of COVID-19-related ARDS is still not completely known, it has been well established that deregulation of the immune host response and a massive inflammatory response, known as a “cytokine storm,” have an important role in pathological damage to the lungs and development of ARDS [4, 5]. Severe lung inflammation causes damage to alveolar epithelial cells and pulmonary microvascular endothelial cells [5]. Plasma sampling from patients with severe COVID-19 revealed high circulating levels of immune-inflammatory markers such as interleukin (IL)-6, IL-1 β , IL-2, IL-7, and IL-17, as well as tumor necrosis factor (TNF)- α [6, 7]. Hence, it is hypothesized that

besides respiratory-support modalities, medical therapies that effectively reduce lung inflammation may be lifesaving in patients with COVID-19-related ARDS [8]. Among many anti-inflammatory agents that have been used to reduce inflammatory responses and mitigate lung damage in severe COVID-19 infection, corticosteroids, due to their accessibility and affordability, have attracted considerable attention around the world [9]. Although previous studies evaluating corticosteroid treatment in cases with viral infection-related ARDS have failed to show consistent benefit [10, 11], emerging evidence strongly supports the potentially beneficial effects of corticosteroids in improving the survival of patients with COVID-19-associated ARDS [9, 12]. The RECOVERY trial was the first trial that provided data on the mortality benefit of dexamethasone therapy in patients with COVID-19 needing oxygen therapy or mechanical ventilation [13]. Since that time, a high number of observational cohort studies and randomized controlled clinical trials with subsequent high-quality meta-analyses have provided robust clinical evidence regarding the benefits of corticotherapy in patients with severe COVID-19 [12, 14].

Although corticosteroids are extensively used in the treatment of patients with severe COVID-19 on respiratory support at present, numerous aspects of their use, such as the preferred agent, optimal dose, and treatment duration, are not yet determined [9]. Regarding corticosteroid agents, dexamethasone at a dose of 6mg once daily for up to 10 days is recommended as the first choice by most guidelines on COVID-19 treatment, and other corticosteroids such as hydrocortisone and methylprednisolone at equivalent doses are considered an alternative when dexamethasone is not available [15]. Although it seems that the benefit of corticosteroids in COVID-19 treatment is a class effect, clinical evidence supporting the use of these alternatives is not conclusive [16]. In some studies, the efficacy of high doses of methylprednisolone has been compared to low to moderate doses of dexamethasone [17–19]. These studies reported that methylprednisolone is superior to dexamethasone; however, the dissimilar doses of the two medicines and different durations of therapy represent potential risks of bias in these studies, which makes interpretation of the findings difficult [20]. Therefore, this prospective controlled clinical trial aimed to compare the efficacy of equivalent doses of methylprednisolone and hydrocortisone to the currently recommended dose of dexamethasone (6mg/day for up to 10 days) in COVID-19 patients with mild to moderate ARDS.

Materials and methods

Study design

We conducted a prospective, randomized, double-blind, three-arm clinical trial on 106 non-ICU hospitalized patients with mild to moderate COVID-19-related ARDS. Our hospital is a tertiary care hospital in the west of Iran with 100 beds dedicated to COVID-19 patients. The trial was designed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The Ethics Committee of Hamadan University of Medical Sciences approved the study protocol (with approval number IR.UMSHA.REC.1399.152), and the trial protocol was registered on 12 May 2020 at the website of the Iranian Registry of Clinical Trials (www.irct.ir), with registration number IRCT20120215009014N354. Written informed consent was obtained from the patients (or their relatives in the case of unconscious patients) after giving detailed information about the study protocol. Given that other studies on COVID-19 patients were underway at our hospital, the first participant was enrolled on 24 August 2020, and the last participant assessment occurred on 17 February 2022.

Study population

Patients were enrolled in the study if they met all of the inclusion criteria, including age between 18 and 75 years; diagnosis of COVID-19 infection confirmed by positive nasopharyngeal polymerase chain reaction testing (RT-PCR) for SARS-CoV-2 infection on nasopharyngeal swab specimens; bilateral pulmonary infiltrates on chest imaging (>50%) compatible with COVID-19 severe pneumonia; mild to moderate ARDS according to the Berlin criteria [21], defined as an arterial oxygen partial pressure to fraction of inspired oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) of 100–300 mmHg, requiring supplemental oxygen administered by simple face mask, nasal cannula, or other similar oxygen-delivery device to maintain oxygen saturation at greater than 93% within the first 48 h of the onset of ARDS; and a signed informed consent form. Patients with one or more of the following exclusion criteria were excluded: previous history of COVID-19 infection; severe ARDS, defined by a $\text{PaO}_2/\text{FiO}_2$ ratio of less than 100 mmHg; an indication for systemic use of higher doses of corticosteroids; hospitalized in the ICU at the time of enrollment; need of immediate mechanical ventilation at the time of enrollment; death or discharge within 48 h of randomized assignment; terminal-stage cancer or other disease; chronic treatment with corticosteroids; immunosuppression or immunosuppressant therapy; home oxygen therapy; chronic liver disease (alanine aminotransferase or aspartate aminotransferase fivefold above the normal upper limit); chronic kidney disease (creatinine clearance

<50 mL/min/1.73 m², estimated by Cockcroft–Gault formula), alcohol and/or substance abuse; psychotic or manic disorder; active infection other than SARS-CoV-2; closed-angle glaucoma; uncontrolled hypertension; decompensated diabetes mellitus; congestive heart failure or severe chronic obstructive pulmonary disease; known hypersensitivity to corticosteroids; enrollment in another experimental treatment protocol; pregnancy or breastfeeding; and unwillingness to participate in the study.

Intervention

Eligible patients were randomly classified into three groups with a 1:1:1 ratio: in group 1 the patients received standard treatment (according to the hospital protocol) plus intravenous dexamethasone at a dose of 6 mg once a day; in group 2 patients received the standard treatment plus intravenous methylprednisolone at a dose of 16 mg twice a day; in group 3 the patients received the standard treatment plus intravenous hydrocortisone at a dose of 50 mg thrice a day. The duration of treatment was up to 10 days. The trial medications were stopped without tapering off at the end of the intervention period. All participants received standard treatment for COVID-19 according to the local hospital protocol, which was based on the Iranian Ministry of Health and international recommendations.

All patients were visited and assessed at least once daily by a pulmonologist and a clinical pharmacist. The severity of the disease and progression of COVID-19 symptoms were assessed daily based on vital signs and symptoms of the patients, laboratory investigations, and arterial blood gas tests. The standard treatment in accordance with the hospital protocol for COVID-19 was provided for all patients as follows: antivirals, antipyretics, supplemental oxygen, antibacterials (when clinical or laboratory data suggested bacterial coinfection), low molecular-weight heparins (enoxaparin) as prophylaxis or treatment according to D-dimer values, electrolytes and hemodynamic support, nutritional support, and stress ulcer prophylaxis. At the discretion of the treating physicians, the patients received remdesivir intravenously at a dose of 200 mg on day one, followed by a 100-mg maintenance dose for up to 9 additional days. Additionally, according to the local hospital protocol, all the studied patients also received vitamins and minerals, including vitamin D3 (1000 IU twice a day), vitamin C (1000 mg twice a day), and zinc (50 mg daily) within their hospitalization period and after discharge for 10 days. As part of our hospital's algorithm, at the discretion of the treating physicians, concomitant use of tocilizumab was allowed in patients who experienced the progression of COVID-19.

Furthermore, when feasible in non-intubated patients, a protocol of early awake prone positioning

was performed by skilled healthcare workers. The treating physicians assessed patients daily in supplemental oxygen requirements and the type of support. Invasive mechanical ventilation was used based on the $\text{PaO}_2/\text{FiO}_2$ ratio and clinical parameters of the patients at the physician's discretion. The patients were transferred to the ICU if their clinical condition deteriorated and/or mechanical ventilation was needed. Extracorporeal membrane oxygenation (ECMO) support was not used in any of the studied patients.

Data collection

Data were carefully recorded from the patients' medical files in a standardized data collection form by a senior medical resident. After review and confirmation by the treating physician, the collected data were transferred into an electronic database. Demographic data, underlying diseases, clinical signs and symptoms at enrollment, laboratory and radiologic findings at enrollment, number of days from symptom onset to enrollment, in-hospital COVID-19 therapies, number of days receiving corticosteroid therapy, and clinical outcomes were collected. All patients were followed from day 0 (enrolment day) up to 28 days post-random assignment or death.

Safety assessment

Adverse events were assessed by an experienced physician who was not affiliated with the study. He reviewed the medical records, signs, symptoms, and laboratory parameters to evaluate any possible adverse events. Adverse events that were thought to be potentially linked to the study medication were recorded as adverse events.

Outcomes

The following outcomes were compared between the treatment groups as primary outcome measures: 1) all-cause 28-day mortality after enrolment; 2) clinical status on day 28 assessed using the World Health Organization (WHO) eight-category ordinal clinical scale (range 0–8, where 0 = no illness, 1–7 = increasing level of care, and 8 = death) [22]; 3) recovered patients, defined as patients who achieved a clinical status ≤ 3 on the WHO eight-category ordinal clinical scale on day 28; and 4) change in $\text{PaO}_2/\text{FiO}_2$ ratios during the first 5 days after the intervention. Secondary endpoints over the 28-day follow-up included: 1) the number of patients needing ICU care; 2) the number of patients needing invasive mechanical ventilation and number of ventilator-free days within 28 days; 3) duration of the ICU stay; 4) duration of hospitalization; and 5) incidence of serious adverse events, including secondary infections, hyperglycemia, clinically important gastrointestinal bleeding, and hypertension. In deceased patients, the number of

ventilator-free days was considered to be 0, and the duration of hospitalization was considered to be 28.

Sample size calculation

According to the results of a clinical trial conducted by Meduri et al. in 2007 [23], the mean (standard deviation, SD) $\text{PaO}_2/\text{FiO}_2$ ratio was reported to be 256 (19) in patients receiving prednisolone. Assuming that this ratio was at least 10 to 15 degrees different in similar treatments, we arrived at a sample size of 35 for each group and a total sample size of 105 at a 95% significance level and 80% statistical power.

Randomization and blinding

Randomization was performed using a stratified block randomization method with a block size of 6 in a 1:1:1 ratio. An independent statistician provided the randomization, and an unblinded hospital pharmacist who was not involved in the care of the study patients or in the entry of outcome data prepared the indistinguishable bags of intravenous solution of the study medications. The study participants, site staff, and researchers were unaware of group allocation. The allocation remained concealed until after the analysis was complete.

Statistical analyses

All analyses were done according to the intention-to-treat (ITT) principle. Descriptive statistics were used for demographic, laboratory, and clinical data. Continuous data were presented as mean (SD) and analyzed using one-way analysis of variance (ANOVA) for testing differences between the groups. The normal distribution of the continuous data was evaluated using the skewness and kurtosis test. Categorical data were presented as both numbers and percentages per treatment arm, and Pearson's chi-square (χ^2) test or Fisher's exact test was used for the percentage comparison. Furthermore, repeated-measure analyses were performed to compare the changes in mean $\text{PaO}_2/\text{FiO}_2$ ratio within the 5-day period after the start of corticosteroid treatment within and between the study groups. For the sake of multiple comparisons, the significance level was corrected using Bonferroni's multiple-testing correction method. A significance level of 0.008 was achieved for six comparisons. Accordingly, p -values less than 0.008 were considered statistically significant. All statistical analyses were performed in the statistical software Stata 16 (StataCorp, College Station, TX, USA).

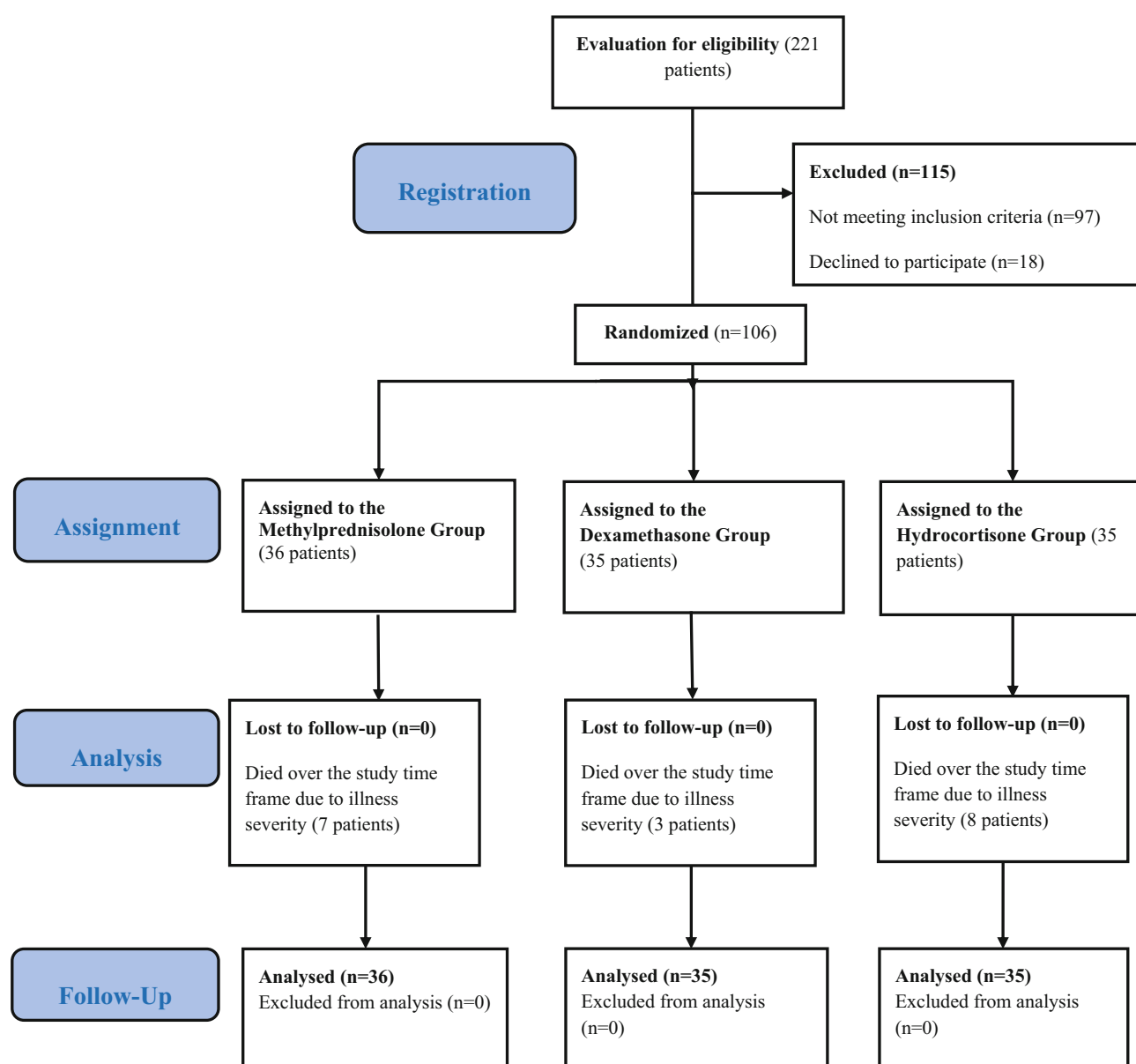


Fig. 1 Flow diagram of the study

Results

Demographics and baseline characteristics

The flow diagram of the study is shown in Fig. 1. Between August 2020 and February 2022, 221 patients with a diagnosis of COVID-19-associated ARDS were assessed for study eligibility, of whom 115 patients were excluded based on the inclusion and exclusion criteria (97 cases) or unwillingness to participate in the study (18 cases). Eventually, 106 patients fulfilling the criteria were randomized to receive either dexamethasone (35 patients), methylprednisolone (36 patients), or hydrocortisone (35 patients). A 28-day follow-up period was completed for all participants, and all the randomized patients were included in the final analysis.

The main baseline demographic and clinical data of the enrolled patients for each treatment group are summarized in Table 1. The baseline characteristics were well matched among the three groups. Mean age of the patients was 62.19 ± 15.01 years, and 56% (60 out of 106 patients) were male. The majority of the patients had at least one comorbidity, and the most common comorbidities were cardiovascular diseases (31.1%) and diabetes mellitus (24.5%). The mean time from symptom onset to corticosteroid therapy was 8.32 ± 3.27 days, and there were no significant differences between the groups in this regard. Almost all patients had bilateral interstitial pneumonia at baseline, based on the high-resolution computed tomography scan findings. The estimated mean \pm SD of $\text{PaO}_2:\text{FiO}_2$ ratio at enrolment time was 141.72 ± 49.20 , 150.03 ± 42.72 , and

Table 1 Baseline demographic and clinical features of the intention-to-treat population

| Variable | Methylprednisolone group (36 patients) | Dexamethasone group (35 patients) | Hydrocortisone group (35 patients) | <i>p</i> -value |
|--|---|--------------------------------------|---------------------------------------|-----------------|
| Age, years, mean \pm SD | 63.05 \pm 16.70 | 62.80 \pm 15.65 | 60.71 \pm 12.62 | 0.776 |
| Sex (M/F), <i>n</i> (%) | 21/15 (58.3/41.7) | 21/14 (60.0/40.0) | 18/17 (51.4/48.6) | 0.779 |
| Time from symptoms onset, mean \pm SD | 8.42 \pm 3.09 | 9.07 \pm 3.94 | 7.57 \pm 2.2.60 | 0.198 |
| General condition at baseline | | | | |
| Temperature, °C, mean \pm SD | 38.09 \pm 0.95 | 37.93 \pm 0.79 | 37.79 \pm 0.86 | 0.363 |
| Heart rate, times/min, mean \pm SD | 87.36 \pm 14.01 | 92.48 \pm 12.19 | 92.94 \pm 14.99 | 0.170 |
| Respiratory rate, times/min, mean \pm SD | 27.16 \pm 3.44 | 26.60 \pm 2.91 | 26.88 \pm 3.07 | 0.743 |
| PaO ₂ /FiO ₂ ratio, mm Hg, mean \pm SD | 141.72 \pm 49.20 | 150.03 \pm 42.72 | 150.03 \pm 42.72 | 0.714 |
| Risk factors for severe diseases | | | | |
| Current smoker, <i>n</i> (%) | 7 (19.4) | 7 (20.0) | 6 (17.1) | 1.000 |
| Cardiovascular disease, <i>n</i> (%) | 11 (30.6) | 12 (34.3) | 10 (28.6) | 0.900 |
| Diabetes, <i>n</i> (%) | 10 (27.8) | 7 (20.0) | 9 (25.7) | 0.782 |
| Respiratory disease, <i>n</i> (%) | 7 (19.4) | 4 (11.4) | 6 (17.1) | 0.715 |
| Neurologic disorder, <i>n</i> (%) | 6 (16.7) | 5 (14.3) | 4 (11.4) | 0.939 |
| Other, <i>n</i> (%) | 7 (19.4) | 9 (25.7) | 4 (11.4) | 0.318 |
| Medication during hospitalization | | | | |
| <i>Anticoagulant</i> | | | | 0.695 |
| Enoxaparin, <i>n</i> (%) | 32 (91.7) | 30 (85.7) | 31 (88.6) | |
| Heparin, <i>n</i> (%) | 3 (8.3) | 5 (14.3) | 4 (11.4) | |
| <i>Remdesivir</i> , <i>n</i> (%) | 32 (88.9) | 29 (82.9) | 29 (82.9) | 0.747 |
| <i>Tocilizumab</i> , <i>n</i> (%) | 5 (13.9) | 4 (11.4) | 4 (11.4) | 0.476 |
| <i>PPIs</i> , <i>n</i> (%) | 27 (75) | 26 (74.3) | 25 (71.4) | 1.000 |
| <i>H2 blockers</i> , <i>n</i> (%) | 9 (25) | 9 (25.7) | 10 (28.6) | 0.962 |
| <i>Antipyretics</i> | | | | 0.819 |
| Acetaminophen, <i>n</i> (%) | 28 (77.8) | 26 (74.3) | 25 (71.4) | |
| Naproxen, <i>n</i> (%) | 8 (22.2) | 9 (25.7) | 10 (28.6) | |
| <i>Supplements</i> | | | | |
| Vitamin D, <i>n</i> (%) | 36 (100) | 35 (100) | 36 (100) | 1.000 |
| Vitamin C, <i>n</i> (%) | 36 (100) | 35 (100) | 36 (100) | 1.000 |
| Melatonin, <i>n</i> (%) | 36 (100) | 35 (100) | 36 (100) | 1.000 |
| Zinc, <i>n</i> (%) | 36 (100) | 35 (100) | 36 (100) | 1.000 |
| <i>Advanced life support modalities</i> | | | | |
| ECMO <i>n</i> (%) | 0 (0) | 0 (0) | 0 (0) | 1.000 |
| RRT | 3 (8.3) | 2 (5.7) | 5 (14.3) | 0.506 |
| Hemoperfusion therapy | 5 (13.9) | 3 (8.6) | 6 (17.1) | 0.597 |
| <i>Days on corticosteroid therapy</i> | 6.75 \pm 1.78 | 6.06 \pm 1.35 | 6.74 \pm 1.48 | 0.103 |

M/F male/female, SD standard deviation, PaO₂/FiO₂ ratio ratio of arterial oxygen partial pressure to fractional inspired oxygen, PPIs proton-pump inhibitors, ECMO extracorporeal membrane oxygenation, RRT renal replacement therapy

146.97 \pm 36.11 mm Hg in the methylprednisolone, dexamethasone, and hydrocortisone groups, respectively. There was no difference between the studied groups regarding the severity of ARDS (*p*-value = 0.714). Most of the studied patients received remdesivir as the main antiviral treatment. The number of patients who received tocilizumab was also similar between the study groups. There were no significant differences among the study groups in terms of other concomitant medications administered in addition to corticosteroid regimens. The mean \pm SD number of days on corticosteroid therapy were 6.75 \pm 1.78, 6.06 \pm 1.35, and 6.74 \pm 1.48 in the methylprednisolone, dexamethasone, and hydrocortisone groups, respec-

tively. No significant difference was observed between the groups in this regard (*p*-value = 0.103).

Primary and secondary clinical efficacy outcomes

Table 2 and Figs. 2 and 3 show the comparison of the primary and secondary clinical efficacy outcomes among the study groups. Although dexamethasone-treated patients had a numerically lower overall mortality during the 28-day follow-up period than methylprednisolone- and hydrocortisone-treated patients (8.6% vs. 19.4% and 22.9%, respectively), no statistically significant differences were found among the studied groups (Table 2; *p*-value = 0.234). In the

Table 2 Primary and secondary study clinical outcomes up to day 28

| Variable | Methylprednisolone group (36 patients) | Dexamethasone group (35 patients) | Hydrocortisone group (35 patients) | <i>p</i> -value |
|--|---|--------------------------------------|---------------------------------------|-----------------|
| Need for mechanical ventilation, <i>n</i> (%) | 8 (22.1) | 5 (14.3) | 10 (28.6) | 0.356 |
| Ventilator-free days, mean \pm SD | 21.38 \pm 11.38 | 24.60 \pm 7.45 | 18.23 \pm 12.44 | 0.053 |
| Need for transfer to ICU, <i>n</i> (%) | 12 (33.3) | 6 (17.1) | 16 (45.7) | 0.034 |
| Duration of ICU stay, days, mean \pm SD | 6.16 \pm 1.75 | 4.83 \pm 1.69 | 6.66 \pm 2.50 | 0.216 |
| Duration of hospitalization, days, mean \pm SD | 10.55 \pm 8.86 | 7.54 \pm 6.48 | 11.57 \pm 9.33 | 0.114 |
| WHO clinical status on day 28, Mean \pm SD | 4.89 \pm 2.21 | 3.74 \pm 2.04 | 5.51 \pm 2.14 | 0.003 |
| 28-day mortality, <i>n</i> (%) | 7 (19.4) | 3 (8.6) | 8 (22.9) | 0.234 |

Note: The *p*-values less than 0.008 based on Bonferroni's multiple testing correction method were considered statistically significant
SD standard deviation, PaO_2/FiO_2 ratio of arterial oxygen partial pressure to fractional inspired oxygen, WHO World Health Organization

same way, mechanical ventilation and ICU care were required in a lower proportion of patients treated with dexamethasone compared to the other two groups. However, the difference between the groups was not statistically significant (*p*-value=0.356 and 0.034, respectively). The mean number of ventilator-free days at 28-day follow-up was similar between

the study groups, with no significant difference (*p*-value=0.053). Further, although patients receiving dexamethasone tended to have a shorter length of ICU and hospital stay compared to those receiving methylprednisolone and hydrocortisone, the differences between groups were not statistically significant (*p*-value=0.216 and 0.114, respectively).

Fig. 2 **a** Comparison of the distribution of clinical status of the groups on day 28 using the eight-point ordinal scale of the World Health Organization (WHO; *p*-value=0.240). **b** Comparison of the proportion of the patients who met recovery criteria on day 28 between the study groups, defined with the WHO clinical status 1, 2, or 3 (*p*-value=0.024). *P*-values lower than 0.008 based on Bonferroni's multiple-testing correction method were considered statistically significant

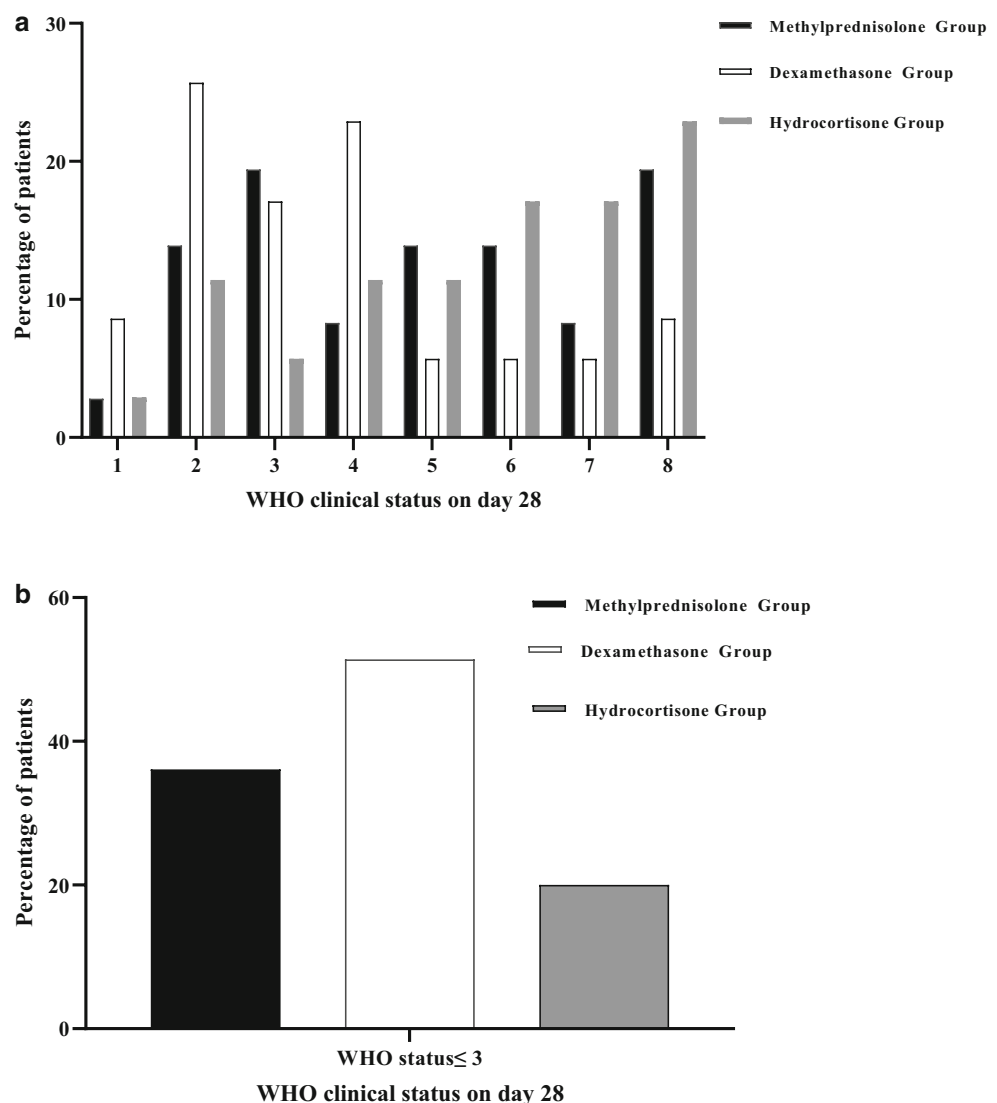


Fig. 3 Change in the mean ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) through different timepoints for the study groups (p -value=0.036). P -values lower than 0.008 based on Bonferroni's multiple-testing correction method were considered statistically significant

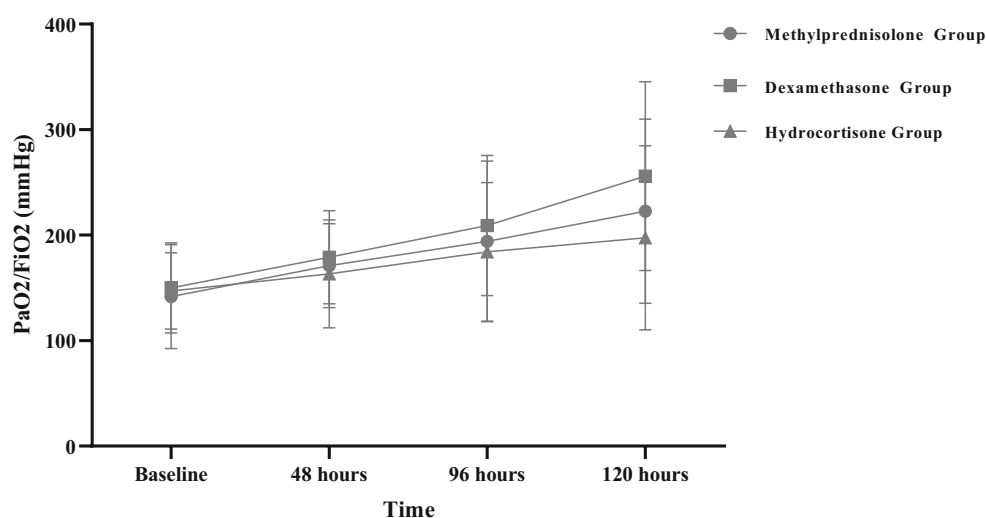


Fig. 2a presents the comparison of the distribution of clinical status on day 28 using the eight-point ordinal scale of the WHO between study groups. No significant difference between the study groups was noted in this regard (Fig. 2a; p -value=0.240). A significant difference was observed among the treatment groups in the mean clinical status score on day 28, as the patients receiving dexamethasone had a lower mean clinical status score (more favorable outcomes) compared to those receiving the methylprednisolone or hydrocortisone regimen (3.74 ± 2.04 in the dexamethasone group vs. 4.89 ± 2.21 and 5.51 ± 2.14 in the methylprednisolone and hydrocortisone groups, respectively; p -value=0.003; Table 2). Although a higher percentage of the patients in the dexamethasone group (51.4% of cases) met the recovery criteria (defined with the WHO clinical status 1, 2, or 3) than of those in the methylprednisolone (36.1% of cases) and hydrocortisone (20.0% of cases) groups, no statistically significant difference was observed between the groups in this regard at the level of significance of less than 0.008 (Fig. 2b; p -value=0.024).

Fig. 3 presents the change in mean PaO_2/FiO_2 ratio during the 5-day period after the start of the corticosteroid treatment. As shown, on days 2 and 3, the improvement in mean PaO_2/FiO_2 ratio was comparable among the study groups, but at the end of day 5, the improvement was greater in the dexamethasone recipients than in the methylprednisolone and hydrocortisone recipients; however, there was no statistically significant difference between the studied groups at the level of significance of less than 0.008 (p -value=0.036).

Safety and adverse events

Concerning the adverse events of corticosteroid treatment, the overall incidence of adverse events did not differ significantly among the treatment groups. The most frequent adverse event in the treatment groups was the occurrence of hyperglycemia, and

no differences were observed between the groups in this regard. Secondary infections in the methylprednisolone, dexamethasone, and hydrocortisone groups occurred in 7 (19.4%), 6 (17.14%), and 6 (17.4%) patients, respectively, and no significant difference was observed between the study groups. Moreover, psychiatric disturbances such as agitation, anxiety, insomnia, irritability, and restlessness occurred in all studied groups with a similar proportion.

Discussion

To the best of our knowledge, our study was the first randomized clinical trial comparing the effectiveness of equivalent doses of dexamethasone, methylprednisolone, and hydrocortisone in hospitalized patients with COVID-19-related ARDS. Based on the results, through 28-day follow-up, there was a trend toward more favorable clinical outcomes including the requirement for ICU care and mechanical ventilation, blood oxygenation, clinical status on day 28, length of ICU and hospital stay, and mortality with dexamethasone treatment compared to methylprednisolone or hydrocortisone treatment; however, a significant difference was only observed in the mean clinical status score at day 28 between the studied groups, which may be due to the small sample size. No significant difference in the incidence of serious adverse events was observed between the study groups. The present data suggest that in treating severe COVID-19, at equivalent doses, dexamethasone might be more effective than methylprednisolone and hydrocortisone in improving clinical status on day 28.

While a well-regulated immune response is essential in controlling SARS-CoV-2 infection, the dysregulated endogenous proinflammatory responses known as cytokine-release syndrome have a crucial role in developing severe forms of the disease, including ARDS, multisystem organ dysfunction, and death [24]. Accordingly, since the start of the pandemic, it has been suggested that immunosuppressive therapy could de-

crease the injurious effects of the inflammatory responses to COVID-19 [25]. Among pharmacological agents, corticosteroids have received the most attention in the treatment of severe COVID-19, which is due to their potent and rapid-onset immunosuppressive and anti-inflammatory effects, as well as their affordability and broad accessibility [20]. At present, it is becoming evident that if timed appropriately, corticosteroid administration could significantly improve clinical outcomes and COVID-19-related morbidity and mortality [14]. Based on recommendations of most international clinical guidelines, corticosteroids are now considered part of the standard of care in managing hospitalized COVID-19 patients needing respiratory support [15, 26, 27]. However, to date, the majority of the efficacy data on supporting corticosteroids in treating COVID-19 are related to dexamethasone [13, 28, 29], and data supporting the use of other glucocorticoids such as hydrocortisone [30, 31] or methylprednisolone [32–34] are not as strong as those evidenced for dexamethasone.

Some studies have compared the efficacy of dexamethasone to methylprednisolone in patients with severe COVID-19. In this regard, Ranjbar et al., in a prospective small triple-blinded randomized controlled trial involving 86 hospitalized adult patients with moderate to severe COVID-19, compared the effects of intravenous dexamethasone at a dose of 6 mg daily for up to 10 days and intravenous methylprednisolone at a dose of 2 mg/kg/day with a daily dose tapered to half of the initial dose every 5 days [17]. They observed that patients receiving methylprednisolone had significantly lower mechanical ventilation requirements, shorter length of hospital stay, and greater clinical status improvement than patients receiving dexamethasone. However, in this trial, methylprednisolone did not reduce mortality compared to dexamethasone [17]. Similarly, Ko et al., also in a retrospective study on 262 COVID-19 patients requiring mechanical ventilation, showed that the use of methylprednisolone at a dose of ≥ 1 mg/kg/d for ≥ 3 days is associated with a 42% lower mortality rate compared with dexamethasone at a dose of ≥ 6 mg for ≥ 7 days [19]. Pinzón et al., in an ambispective cohort study on 216 cases with severe COVID-19 pneumonia, found that a high dose of methylprednisolone of 250 to 500 mg every day for 3 days followed by oral prednisone (50 mg daily for 14 days) is superior to dexamethasone at a dose of 6 mg for 7–10 days. In their study, compared to dexamethasone, methylprednisolone resulted in a statistically significant decrease in the serum level of lactate dehydrogenase, C-reactive protein, and d-dimer, and more improvement in the rate of ICU admission and recovery time [18]. In contrast to our findings, the results of the mentioned studies show the superiority of methylprednisolone over dexamethasone in treating severe COVID-19 infection. These contradictory results may be due to the use of nonequivalent doses

of two medications in the mentioned studies. Indeed, their results indicated the superiority of high doses of methylprednisolone over low to moderate doses of dexamethasone in treating severe COVID-19 infection. Fatima et al., in a quasi-experimental, interventional study including 100 cases with moderate to severe COVID-19, compared the efficacy of intravenous dexamethasone at a dose of 8 mg/day with intravenous methylprednisolone at a dose of 1 mg/kg/day for 5 days [35]. They reported that both dexamethasone and methylprednisolone have equal efficacy in improving the biochemical and clinical outcomes of patients with moderate to severe COVID-19 [35]. However, in this study, like the other studies mentioned above, nonequivalent doses of two medications were compared. Moreover, in Fatima et al.'s study, the patients treated with dexamethasone were more critical than those treated with methylprednisolone, which might represent a risk of bias in their findings.

On the contrary, the results of a large retrospective study conducted by Mora-Luján et al. [36] on severe, non-critically ill COVID-19 cases demonstrated that treatment with dexamethasone at a dose of 6 mg/day for 10 days is more effective than 3 days of treatment with high-dose methylprednisolone pulses (≥ 100 mg/day) in reducing in-hospital mortality and the need for invasive mechanical ventilation and ICU admission. The authors concluded that the beneficial effects of corticosteroid in treating severe COVID-19 infection are time dependent, as the duration of corticotherapy should be a minimum of 10 days [36]. Consistent with these findings, Oganessian et al. showed that a short 3-day dexamethasone treatment is not superior to the standard of care in lowering the 28-day mortality rate [37]. Similar to our study, Rana et al., in a retrospective quasi-experimental study, assessed the effectiveness of almost equivalent doses of dexamethasone (8 mg twice daily) and methylprednisolone (40 mg twice daily) in patients with moderate COVID-19-related ARDS [38]. Although they used a higher dose of both medications for a shorter period, their study also revealed that at an equivalent dose, dexamethasone is more effective than methylprednisolone in improving oxygenation and reducing ventilation dependency in COVID-19-related ARDS [38].

The data relating to the clinical use of hydrocortisone in COVID-19 treatment and its potential benefits are limited to a few small trials [30, 31, 39]. Some of these trials were terminated early after the release of the favorable findings of the RECOVERY trial [31, 39]. The WHO meta-analysis, including three trials evaluating hydrocortisone in COVID-19 treatment, demonstrated a non-statistically significant trend toward lower 28-day mortality in patients treated with hydrocortisone compared to those treated with placebo [14]. These trials as individuals also failed to demonstrate a clear mortality benefit from using hydrocortisone in COVID-19 [30, 31]. Only one pub-

lished study has directly compared the efficacy of hydrocortisone to other corticosteroids. Plessis et al., in their retrospective cohort study, compared the clinical outcomes of patients with severe COVID-19 infection treated with high-dose hydrocortisone (100 to 200 mg every 6 h), high-dose methylprednisolone (40 mg every 12 h), and a lower dose of dexamethasone (8 mg once daily) given for 10–14 days [40]: there was no significant difference in the clinical outcomes of patients treated with each of these medication regimens. It was suggested that both methylprednisolone and hydrocortisone could be used as alternatives to dexamethasone in the treatment of severe COVID-19.

Considering the present results and the studies mentioned above, dexamethasone at an equivalent dose may be more effective than methylprednisolone and hydrocortisone in improving clinical outcomes in patients with severe COVID-19. It may be concluded that a higher dose of methylprednisolone and hydrocortisone compared to dexamethasone is required in the treatment of COVID-19 patients to have similar clinical benefits. This may be related to differences in the pharmacodynamic and pharmacokinetic profiles of these medicines. Corticosteroids differ with regard to their glucocorticoid and mineralocorticoid effects. Dexamethasone has much higher glucocorticoid potency and negligible mineralocorticoid effects compared to methylprednisolone and hydrocortisone. Indeed, dexamethasone exerts anti-inflammatory effects without mineralocorticoid stimulation [41]. Thus, it is thought that the negligible mineralocorticoid activities of dexamethasone may be beneficial in ARDS patients [42]. Further, considering the long biological half-life of dexamethasone compared to other corticosteroids, its pharmacological effects are long lasting, allowing for slow therapy taper [41].

Due to the limitations of the present study, its results must be interpreted with caution. The main limitation of the present study was the relatively small number of participants, which reduced the power of our study to detect a significant difference in several study endpoints between the groups, and we were unable to perform additional analyses in the subgroups of the patients. Moreover, due to the strict inclusion and exclusion criteria of our study, the enrolled cases were a highly selected group of COVID-19 patients, and many patients requiring treatment were excluded. Additionally, it was a single-center study, and management and outcomes do not necessarily reflect those at other centers. External validation is necessary to confirm our findings. Another limitation of the present study is the lack of a control group (patients not receiving any corticosteroids) due to ethical considerations. Further, the vast majority of patients in this trial also received remdesivir as part of the standard treatment of the hospital, which might limit the assessment of the real effect of the study medication on clinical outcomes, although there were no significant

differences between the groups regarding the proportion of patients treated with remdesivir.

Conclusion

The present data suggest that dexamethasone at an equivalent dose might be more effective than methylprednisolone and hydrocortisone in improving clinical status on day 28 in patients with severe COVID-19 infection. The rational conclusion is that compared to dexamethasone, higher doses of methylprednisolone and hydrocortisone may be required for treating patients with severe COVID-19 infection. However, larger multicenter trials are required to confirm these results.

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Declarations

Conflict of interest A. Taher, M. Lashkari, F. Keramat, S.H. Hashemi, L. Sedighi, J. Poorolajal, and M. Mehrpooya declare that they have no competing interests.

Ethical standards The trial protocol was according to the Declaration of Helsinki as revised in 1989, and the study protocol was approved by the research and ethics committee at Hamadan University of Medical Sciences (IR.UMSHA.REC.13999.152). Patients (or relatives in case of unconscious patients) provided written informed consent.

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